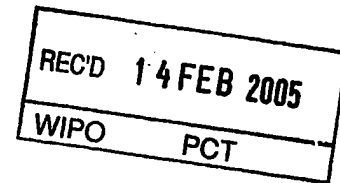




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Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Crystalline forms of Rizatriptan benzoate

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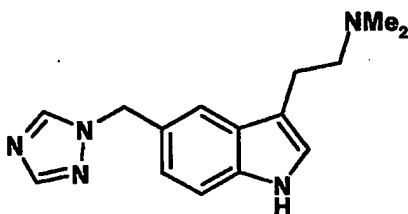
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Crystalline forms of Rizatriptan benzoate

The present invention is directed to crystalline forms of Rizatriptan benzoate, processes for the preparation thereof and pharmaceutical compositions comprising these crystalline forms.

The present invention relates to novel crystalline forms of Rizatriptan benzoate. Rizatriptan benzoate is known by the chemical name, N,N-dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-3-ethanamine benzoate. Rizatriptan has the following formula:



Rizatriptan benzoate is a selective 5-hydroxytryptamine _{1B/1D} (5-HT_{1B/1D}) receptor agonist, and is marketed as an oral formulation for acute treatment of migraine.

Processes for the preparation of Rizatriptan benzoate are disclosed in the patents GB-A-2315673, WO-A-95/32197, EP-A-497512, and in the publications by Cheng-yi Chen et al. in Tetrahedron Letters (1994), vol. 35, pages 6981-6984 and L.J. Street et al. in Journal of Medicinal Chemistry (1995), vol. 38, pages 1799-1810. In the processes described in the above mentioned patents and publications Rizatriptan benzoate is isolated from ethanol as a white solid with a melting point of 178-180°C. However, there is still a need to produce Rizatriptan benzoate in a reproducible, pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications. Furthermore, it is known that pharmaceutical substances can exhibit polymorphism. Polymorphism is commonly defined as the ability of any substance to have two or more different crystal structures. Drug substances may also encapsulate solvent molecules when crystallized. These solvates or hydrates are referred to as pseudopolymorphs. It is also possible that the amorphous form is encountered. Different polymorphs, pseudopolymorphs or the amorphous form differ in their physical properties such as melting point, solubility etc. These can appreciably influence pharmaceutical properties such as dissolution rate and bioavailability. It is also

economically desirable that the product is stable for extended periods of time without the need for specialized storage conditions. It is therefore important to evaluate polymorphism of drug substances. In addition, the discovery of new crystalline polymorphic forms of a drug enlarges the repertoire of materials that a formulation scientist has with which to design a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristics.

It has now surprisingly been found that Rizatriptan benzoate exhibits polymorphism and can be crystallized from several organic solvents giving Rizatriptan benzoate reproducible in a very stable, well-defined crystalline form, herein designated as Form A, whereas crystallization from 1-butanol or from mixtures of ethyl acetate with an alkane results in a meta-stable crystalline form, herein designated as Form B.

Accordingly, the present invention is directed to the polymorphic Forms A and B of Rizatriptan benzoate.

One object of the invention is a crystalline polymorph of N,N-dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-3-ethanamine benzoate, herein designated as Form A, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) and in 2θ as given in Table 1 (vs = very strong intensity, s = strong intensity, m = medium intensity, w = weak intensity, vw = very weak intensity).

Table 1: d-spacings and 2θ angles for Form A.

Angle °2θ	d-spacing (Å)	Qualitative Relative Intensity
8.3	10.7	w
9.2	9.6	w
11.6	7.6	w
12.9	6.9	w
13.6	6.5	vw
14.5	6.1	vw
15.9	5.56	m
16.2	5.47	vw
16.5	5.36	w

17.1	5.19	s
17.7	5.00	m
17.9	4.95	m
18.4	4.81	w
18.9	4.70	vs
19.3	4.59	w
20.3	4.38	vw
21.1	4.22	s
22.2	4.00	s
22.8	3.91	w
23.4	3.81	w
23.9	3.72	w
24.2	3.68	vw
25.0	3.56	s
26.2	3.40	m
27.2	3.27	vw
28.2	3.16	vw
28.9	3.09	w
29.3	3.05	vw
31.1	2.87	vw
31.7	2.83	w
32.0	2.79	vw
33.4	2.68	vw
34.1	2.63	vw
34.7	2.59	vw
36.0	2.50	vw
37.1	2.42	vw
37.9	2.38	vw
39.5	2.28	vw

Another object of the invention is a crystalline polymorph of N,N-dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-3-ethanamine benzoate, herein designated as Form B, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed

in d-values (Å) and in 2θ as given in Table 2 (vs = very strong intensity, s = strong intensity, m = medium intensity, w = weak intensity, vw = very weak intensity).

Table 2: d-spacings and 2θ angles for Form B.

Angle 2θ	d-spacing (Å)	Qualitative Relative Intensity
7.8	11.3	vw
8.5	10.4	vs
8.9	9.9	vw
11.3	7.8	vw
11.6	7.6	vw
13.2	6.7	vw
13.5	6.6	vw
15.0	5.89	m
15.7	5.64	vw
16.3	5.45	s
16.6	5.35	m
17.1	5.18	w
17.5	5.07	vw
17.9	4.95	s
18.9	4.71	s
20.0	4.45	m
20.4	4.36	m
21.0	4.23	w
21.2	4.18	w
22.4	3.97	m
22.7	3.92	m
22.9	3.89	m
23.6	3.76	m
24.0	3.70	m
24.4	3.65	vw
25.5	3.50	w
25.8	3.45	w

26.4	3.38	vw
27.0	3.30	vw
27.8	3.21	vw
28.2	3.16	vw
28.7	3.11	vw
32.9	2.72	w
34.7	2.59	vw

The polymorphic Form A of Rizatriptan benzoate is especially characterized by an X-ray powder diffraction pattern as depicted in Figure 1, whereas the polymorphic Form B of Rizatriptan benzoate is especially characterized by an X-ray powder diffraction pattern as depicted in Figure 2.

Furthermore, the present invention is directed to processes for the preparation of Form A and Form B of Rizatriptan benzoate.

Form A can be generally prepared by crystallization from cooled solutions of Rizatriptan benzoate in an organic solvent, or mixtures of organic solvents, or a mixture of an organic solvent with a cosolvent selected from hydrocarbons and ethers or water. Preferably the organic solvent is an alcohol, e.g. a C₁-C₈alcohol, preferably a primary alcohol, like methanol, 1-butanol or 1-octanol, or esters like ethyl acetate, or a ketone solvent, like acetone or methyl isobutyl ketone. Preferred cosolvents are selected from C₅-C₈alkanes such as hexane and/or heptane and ethers such as diethylether, ethyl-butyl ether, ethyl-propyl ether, dipropylether, propyl-butyl ether, dibutylether, tetrahydrofuran, dioxan. Advantageous mixtures include those of an acetate with an alkane, e.g. a C₅-C₈alkane like hexane or heptane. Preferably these solutions are cooled from temperatures of about 20 to 100°C down to temperatures of about -20° to 10°. Most preferably from temperatures of about 50 to 80°C down to temperatures of about 0°C to 5°C. Form A can also be generally prepared by evaporation of aqueous solutions, or by evaporation of solutions of Rizatriptan benzoate in a mixture of an organic solvent with water, e.g. by applying reduced pressure (vacuum). Preferably the organic solvent is an alcohol, like 2-propanol or 1-butanol, and the amount of water is ranging from 1% to 50%, most preferably about 10% to 20%. Form A can also be generally prepared by adding an organic solvent to a solution of Rizatriptan

benzoate in a mixture of an organic solvent and water. Preferably the organic solvent is an alcohol, like 2-propanol, or a ketone solvent, like acetone, or tetrahydrofuran.

Form B can be generally prepared by fast crystallization, for example by addition of a solution of Rizatriptan benzoate in an alcohol, or mixtures of an alcohol with another organic solvent, to a non-solvent or vice versa. The alcohol solvent is preferably methanol, and can be mixed with other organic solvents like acetates, preferably ethyl acetate. Examples of non-solvents are alkanes, e.g. C₅-C₈alkanes, preferably hexane or heptane. The precipitated Rizatriptan benzoate Form B is preferably isolated by filtration and dried under vacuum. Form B can also be generally prepared by evaporation of an alcoholic solution. Preferably the alcohol is 1-butanol or 2-propanol.

In the above mentioned processes small amounts of seeding crystals of the desired crystalline form may be added to the reaction mixture. Preferably small amounts are about 1 to 20 weight%, more preferably about 5 weight%. Seeding crystals may be added before or, where appropriate, after the step initiating the crystallization (e.g. cooling, addition of non-solvent etc. as described above). Addition before initiating the crystallization is of specific technical interest.

Another object of the present invention are pharmaceutical compositions comprising an effective amount of crystalline polymorphic Form A or B of Rizatriptan benzoate, and a pharmaceutically acceptable carrier.

These polymorphic forms may be used as single component or as mixtures with other crystalline forms or the amorphous form.

As to the novel polymorphic forms of Rizatriptan benzoate it is preferred that these contain 25-100% by weight, especially 50-100% by weight, of at least one of the novel forms, based on the total amount of Rizatriptan benzoate. Preferably, such an amount of the novel polymorphic forms of Rizatriptan benzoate is 75-100% by weight, especially 90-100% by weight. Highly preferred is an amount of 95-100% by weight.

The compositions of the invention include powders, granulates, aggregates and other solid compositions comprising at least one of the novel forms. In addition, the compositions that

are contemplated by the present invention may further include diluents, such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl, cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents like calcium carbonate and calcium diphosphate and other diluents known to the pharmaceutical industry. Yet other suitable diluents include waxes, sugars and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

Further excipients that are within the contemplation of the present invention include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes. Excipients that also may be present in the solid compositions further include disintegrants like sodium starch glycolate, croscovidone, low-substituted hydroxypropyl cellulose and others. In addition, excipients may include tableting lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

Dosage forms include solid dosage forms, like tablets, powders, capsules, suppositories, sachets, troches and lozenges as well as liquid suspensions and elixirs. While the description is not intended to be limiting, the invention is also not intended to pertain to true solutions of Rizatriptan benzoate whereupon the properties that distinguish the solid forms of Rizatriptan benzoate are lost. However, the use of the novel forms to prepare such solutions is considered to be within the contemplation of the invention.

Capsule dosages, of course, will contain the solid composition within a capsule which may be made of gelatin or other conventional encapsulating material. Tablets and powders may

be coated. Tablets and powders may be coated with an enteric coating. The enteric coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl-cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

Preferred unit dosages of the pharmaceutical compositions of this invention typically contain from 1 to 50 mg of the novel Rizatriptan benzoate forms or mixtures thereof with each other or other forms of Rizatriptan benzoate. More usually, the combined weight of the Rizatriptan benzoate forms of a unit dosage are from 2.5 mg to 30 mg, for example 5 or 10 mg.

The following Examples illustrate the invention in more detail. Temperatures are given in degrees Celsius. If not stated otherwise, ambient atmosphere or room temperature is in the range 20-25°C. Abbreviations and symbols used in the Examples and elsewhere:

TBME: tert.-butyl-methyl ether

1 Å stands for 10^{-10} m.

Example 1: Preparation of Form A

47 mg of rizatriptan benzoate are suspended in 35 ml TBME and heated to 60°C, then 0.2 ml methanol are added at 60°C to increase the solubility. The almost clear solution is filtered through a 0.22 µm Millipore filtration unit. Then the filtrated solution is cooled to room temperature and near room temperature the still clear solution is seeded with 2 mg rizatriptan benzoate Form A. The temperature is further reduced to 5°C, and the obtained suspension is stored at 5°C for about 24 hours, before the solid is separated by filtration. The obtained white solid contains crystals with a needle shaped crystal habit, yield 22 mg Form A. The obtained crystal Form A is characterized by an X-ray powder diffraction pattern as shown in Figure 1.

Example 2: Preparation of Form A

70 mg of rizatriptan benzoate are dissolved in 10 ml 1-butanol at 60°C. The temperature of the clear solution is reduced to room temperature and seeded with 2 mg rizatriptan

benzoate Form A. The obtained suspension is further cooled to 5°C and stored at this temperature for about 2 hours. The obtained white crystals were separated by filtration, yielding 20 mg Form A in form of white flakes. The obtained crystal Form A is characterized by an X-ray powder diffraction pattern as shown in Figure 1.

Example 3: Preparation of Form A

21 mg rizatriptan benzoate are dissolved in a mixture of 8.5 ml ethyl acetate and 8.5 ml heptane at 70°C. The clear solution is cooled to room temperature and seeded with 1 mg rizatriptan benzoate Form A. After about 30 minutes storage at 5°C, needle-like crystals start to grow, and the suspension is filtered after 18 hours, yielding 12 mg Form A. The obtained crystal Form A is characterized by an X-ray powder diffraction pattern as shown in Figure 1.

Example 4: Preparation of Form A

24 mg rizatriptan benzoate are dissolved in 3 ml 1-octanol at 70°C and the obtained solution is cooled to room temperature. About 40 minutes after seeding with 1 mg rizatriptan benzoate Form A the solution becomes turbid due to the progress of the crystallization process. After 20 hours of further phase equilibration, the suspension is filtered, and about 10 mg of Form A as a white powder is obtained after filtration and drying. The obtained crystal Form A is characterized by an X-ray powder diffraction pattern as shown in Figure 1.

Example 5: Preparation of Form A

An aqueous solution of rizatriptan benzoate (10 mg/ml) was evaporated on a watch glass at ambient atmosphere (room temperature), yielding Form A quantitatively. The obtained crystal Form A is characterized by an X-ray powder diffraction pattern as shown in Figure 1.

Example 6: Preparation of Form A

A solution of 10 mg rizatriptan benzoate in a mixture of 1 ml 2-propanol and 0.1 ml water is evaporated in a glass vial at ambient atmosphere, yielding Form A quantitatively. The obtained crystal Form A is characterized by an X-ray powder diffraction pattern as shown in Figure 1.

Example 7: Preparation of Form A

13 mg rizatriptan benzoate are dissolved in 2 ml 1-butanol at 60°C. The clear solution was cooled to room temperature and seeded with 0.5 mg crystals of rizatriptan benzoate Form A. After addition of 13 ml heptane precipitation starts. After filtration of the obtained suspension, 10 mg of Form A was obtained as a white powder. Microscopic inspection of the white powder shows that the obtained crystals are plate like particles. The obtained crystal Form A is characterized by an X-ray powder diffraction pattern as shown in Figure 1.

Example 8: Preparation of Form B

75 mg of rizatriptan benzoate are dissolved in 0.5 ml methanol at 60°C. The solution is added to 14 ml ethyl acetate at room temperature, and subsequently 10 ml heptane are added to the clear solution. After about 15 minutes after addition of heptane, crystallization is observed when clusters of needles start to grow. The obtained suspension is further stored at room temperature for one hour and filtered through a glass filter. 32 mg of Form B as a white solid were obtained are dried at room temperature. The obtained crystal Form B is characterized by an X-ray powder diffraction pattern as shown in Figure 2.

Example 9: Preparation of Form B

130 mg of rizatriptan benzoate are dissolved in 0.5 ml methanol at 60°C. The prepared solution is added to 14 ml ethyl acetate at -18°C before seeding with 5 mg of rizatriptan benzoate Form B. After about one minute the precipitation starts. The obtained suspension is filtered, and the obtained white solid is dried in an air flow, yielding 82 mg Form B. The obtained crystal Form B is characterized by an X-ray powder diffraction pattern as shown in Figure 2.

Example 10: Preparation of Form B

27 mg of rizatriptan benzoate are dissolved in 7 ml 1-butanol at 50°C. This solution is filtered through a 0.22 µm Millipore filter, cooled to room temperature, and allowed to evaporate at ambient atmosphere. After evaporation of the solvent, Form B is obtained quantitatively. The obtained crystal Form B is characterized by an X-ray powder diffraction pattern as shown in Figure 2.

Example 11: Preparation of Form B

A solution of rizatriptan benzoate in 2-propanol (2 mg/ml) is heated to 60°C, filtered through a 0.22 µm Millipore filter and seeded 5 wt% rizatriptan benzoate Form B. The solution with

the seed crystals is allowed to evaporate at ambient atmosphere. After evaporation of the solvent rizatriptan benzoate Form B is obtained quantitatively. The obtained crystal Form B is characterized by an X-ray powder diffraction pattern as shown in Figure 2.

Example 12: Preparation of Form A

7 mg rizatriptan benzoate Form A and 7 mg Form B are suspended in 1 ml ethyl acetate, and stirred 16 hours at 25°C. After filtration, a white powder is obtained. Characterization by X-ray powder diffraction shows that rizatriptan benzoate Form A is obtained, showing that Form A is the thermodynamically most stable form and that Form B is a metastable form.

X-ray powder diffraction measurements were performed on a Philips 1710 powder X-ray diffractometer using Cu K α radiation (Cu K α_1 = 1.54060Å). The X-ray source is operated at 45 kV and 45 mA. Spectra are recorded at a step size of 0.02° with a counting time of 2.4 seconds per step. The accuracy of the 2 theta values of conventionally recorded powder X-ray diffraction patterns is generally +/- 0.1-0.2°. For sample preparation, about 40 mg of substance was prepared into circular shaped quartz sample holders of 0.5 mm depth and 10 mm width.

Brief description of the drawings

Figure 1 is a characteristic X-ray powder diffraction pattern for Form A.

Figure 2 is a characteristic X-ray powder diffraction pattern for Form B.

Claims

1. A crystalline polymorph Form A of N,N-dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-3-ethanamine benzoate which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) at 5.19 (s), 4.70 (vs), 4.22 (s), 4.00 (s), 3.56 (s); specifically 5.56 (m), 5.19 (s), 5.00 (m), 4.95 (m), 4.70 (vs), 4.22 (s), 4.00 (s), 3.56 (s), 3.40 (m); more specifically 10.7 (w), 9.6 (w), 7.6 (w), 6.9 (w), 5.56 (m), 5.36 (w), 5.19 (s), 5.00 (m), 4.95 (m), 4.81 (w), 4.70 (vs), 4.59 (w), 4.22 (s), 4.00 (s), 3.91 (w), 3.81 (w), 3.72 (w), 3.56 (s), 3.40 (m), 3.09 (w), 2.83 (w), as depicted in Figure 1; wherein (vs) stands for very strong intensity; (s) stands for strong intensity; (m) stands for medium intensity; (w) stands for weak intensity.
2. A crystalline polymorph Form B of N,N-dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-3-ethanamine benzoate which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) at 10.4 (vs), 5.45 (s), 4.95 (s), 4.71 (s); specifically 10.4 (vs), 5.89 (m), 5.45 (s), 5.35 (m), 4.95 (s), 4.71 (s), 4.45 (m), 4.36 (m), 3.97 (m), 3.92 (m), 3.89 (m), 3.76 (m), 3.70 (m); more specifically 10.4 (vs), 5.89 (m), 5.45 (s), 5.35 (m), 5.18 (w), 4.95 (s), 4.71 (s), 4.45 (m), 4.36 (m), 4.23 (w), 4.18 (w), 3.97 (m), 3.92 (m), 3.89 (m), 3.76 (m), 3.70 (m), 3.50 (w), 3.45 (w), 2.72 (w), as depicted in Figure 2; wherein (vs) stands for very strong intensity; (s) stands for strong intensity; (m) stands for medium intensity; (w) stands for weak intensity.
3. A process for the preparation of a crystalline polymorph according to claim 1, in which a solution of Rizatriptan benzoate is cooled and the solution is in an organic solvent or in a mixture of organic solvents or in a mixture of an organic solvent with a cosolvent selected from hydrocarbons and ethers or water.
4. A process according to claim 3 in which the organic solvent is selected from an alcohol, a ketone, an acetate.
5. A process according to claim 3 where in the mixture of an organic solvent with a cosolvent, the cosolvent is selected from C₅-C₈alkanes, diethylether, ethyl-butyl ether, ethyl-propyl ether, dipropylether, propyl-butyl ether, dibutylether, tetrahydrofuran,

dioxan; and the mixture preferably is mixture of an acetate and a C₅-C₈alkane such as ethyl acetate and heptane.

6. A process according to claim 3 in which the solution is cooled from a temperature of about 20° to 100°C down to about -20°C to 0°C; preferably from a temperature of about 50° to 80°C down to about 0°C to 5°C.
7. A process for the preparation of a crystalline polymorph according to claim 1, in which an aqueous solution of Rizatriptan benzoate or a solution of Rizatriptan benzoate in a mixture of water and an organic solvent is evaporated to dryness.
8. A process according to claim 7 in which the organic solvent is an alcohol, preferably 2-propanol or 1-butanol.
9. A process according to claim 7 in which the amount of water is ranging from 1 to 90 volume%, preferably from 10 to 30 volume%.
10. A process for the preparation of a crystalline polymorph according to claim 1, in which an organic solvent is added to a solution of Rizatriptan benzoate in a mixture of an organic solvent and water, and where the organic solvent preferably is an alcohol, an ether or a ketone such as 2-propanol, acetone or tetrahydrofuran.
11. A process for the preparation of a crystalline polymorph according to claim 2, in which Rizatriptan benzoate is obtained by fast crystallization.
12. A process for the preparation of a crystalline polymorph according to claim 2, in which a solution of Rizatriptan benzoate in an alcohol, or in a mixture of an alcoholic and another organic solvent, is added to a non-solvent; or in which a non-solvent is added to a solution of Rizatriptan benzoate in an alcohol or in a mixture of an alcohol with another organic solvent.
13. A process according to claim 12 in which the solution of Rizatriptan benzoate is in a mixture of an alcohol with an acetate; preferably methanol and ethyl acetate.

14. A process according to claim 12 in which the non-solvent is an alkane, preferably hexane or heptane.
15. A process for the preparation of a crystalline polymorph according to claim 2, in which a solution of Rizatriptan benzoate in an alcohol, preferably in 2-propanol or 1-butanol, is evaporated to dryness.
16. A process according to any of the claims 3 to 15, wherein seeding is carried out with crystals of the desired crystalline polymorph.
17. A process according to any of the claims 3 to 16 in which the solution of Rizatriptan benzoate is prepared in situ or is prepared upon reaction of rizatriptan free base with benzoic acid.
18. A pharmaceutical composition comprising an effective amount of a crystalline polymorphic form according to any of claims 1 to 2, and a pharmaceutically acceptable carrier.

Abstract

The present invention is directed to the novel polymorphic Form A and Form B of Rizatriptan benzoate, processes for the preparation thereof and pharmaceutical compositions comprising these crystalline forms.

1 / 2

Figure 1:

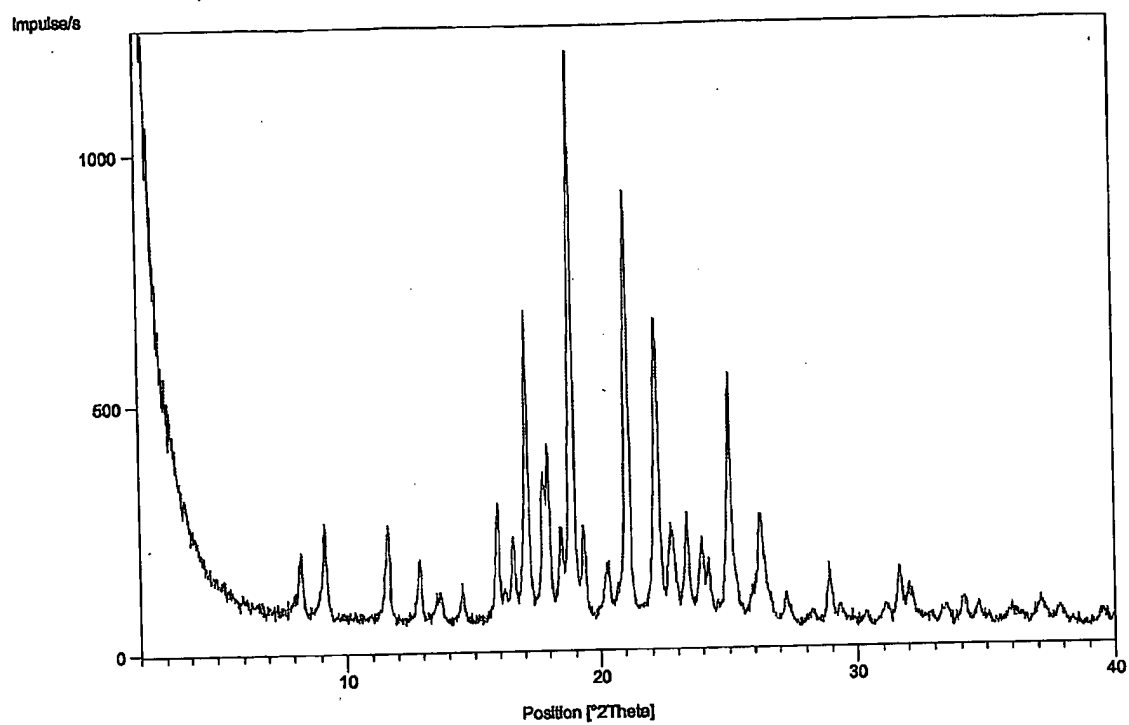
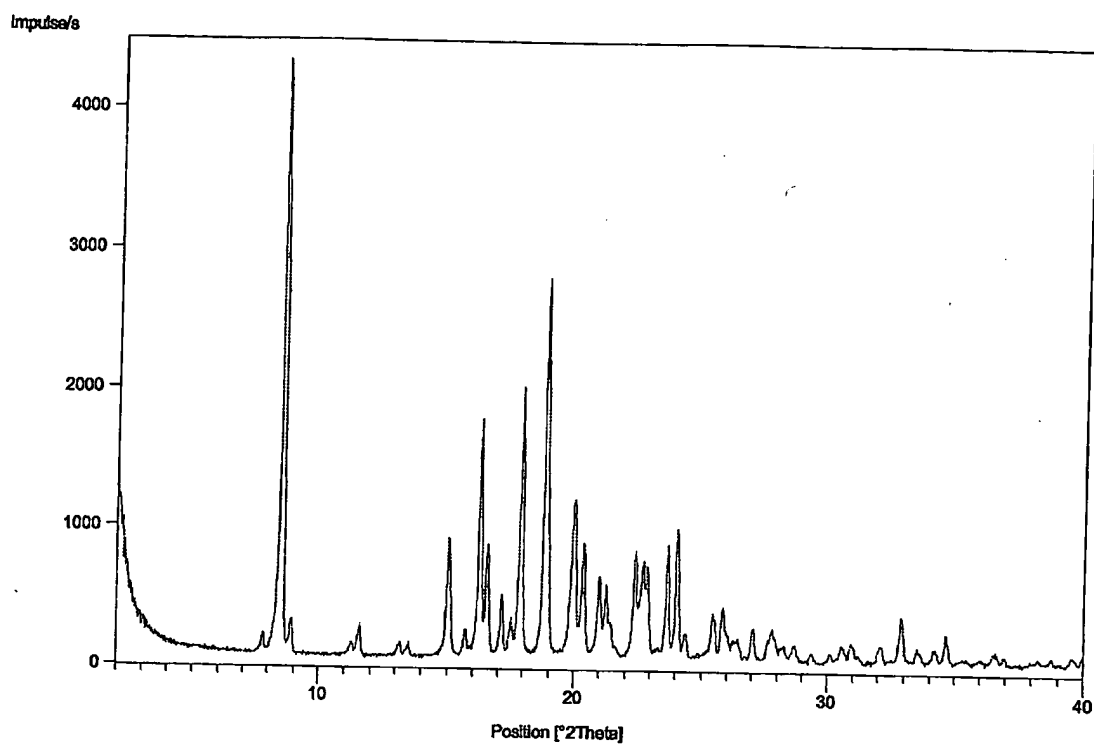


Figure 2:



PCT/EP2005/000034

